


# Predicting the impact of control strategies on the tuberculosis burden in South and North Korea using a mathematical model

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## ABSTRACT

**Background** Among high-income countries, South Korea has a considerable tuberculosis (TB) burden; North Korea has one of the highest TB burdens in the world. Predicting the impact of control strategies on the TB burden can help to efficiently implement TB control programmes.

**Methods** We designed a deterministic compartmental model of TB in Korea. After calibration with notification of incidence data from South Korea, the TB burden for 2040 was predicted according to four different intervention strategies: latent TB infection (LTBI) treatment, rapid diagnosis, active case-finding and improvement of the treatment success rate. North Korea's burden in 2040 was similarly estimated by adjusting the model parameters.

**Results** In South Korea, the number of patients with drug-susceptible TB (DS-TB) and multidrug-resistant TB (MDR-TB) were predicted to be 27 581 and 625, respectively, in 2025. Active case-finding would lower DS-TB by 6.2% and MDR-TB by 26.7%, respectively, in 2040. The improvement in the success rate of DS-TB treatment would reduce the MDR-TB burden by 34.5%. In North Korea, the number of patients with DS-TB and MDR-TB are, respectively, predicted to be 77 629 and 5409 in 2025. Active case-finding would reduce DS-TB by 22.2% and MDR-TB by 69.7%. LTBI treatment would reduce DS-TB by 20.6% and MDR-TB by 38.6%.

**Conclusion** The impact of control strategies on the TB burden in South and North Korea was investigated using a mathematical model. The combined intervention strategies would reduce the burden and active case-finding is expected to result in considerable reduction in both South and North Korea.

## INTRODUCTION

Tuberculosis (TB), a communicable disease that is a major cause of ill health, is one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent.<sup>1</sup> Despite efforts to eliminate TB based on the WHO's END TB strategy<sup>2</sup> and a political declaration at a UN high-level meeting,<sup>3</sup> an estimated 10 million people suffered from TB in 2018. Moreover, drug-resistant

## WHAT IS ALREADY KNOWN?

- ⇒ Tuberculosis (TB) is a significant challenge in the Korean peninsula. North Korea is one of the 30 countries with the highest TB and drug resistant TB burdens and TB incidence in South Korea is considerable among high income countries.
- ⇒ There are relatively few studies on the modelling of drug resistant TB incorporating to the drug susceptible TB.

## WHAT ARE THE NEW FINDINGS?

- ⇒ Using reported national TB data from South and North Korea, local epidemiologic parameters, we developed a dynamic model for drug susceptible (DS) and multidrug-resistant (MDR) TB in South and North Korea. DS and MDR-TB continuously decreased and active case finding (ACF) and the improvement of DS-TB treatment were effective in reducing TB burdens in South Korea. In North Korea, MDR-TB burdens increased even several interventions. ACF and improvement of diagnostics and DS-TB treatment were effective in reducing MDR-TB in North Korea.

## WHAT DO THE NEW FINDINGS IMPLY?

- ⇒ The DS-TB and MDR-TB incorporating model we developed can help estimate the impact of TB control strategies comprehensively. In resource limited settings such as North Korea, to overcome the burden of drug resistant TB, a sustainable and comprehensive TB control strategy that focuses on both DS-TB and MDR-TB is necessary.

TB continues to be a threat to public health. Only 39% of the estimated 484 000 rifampin-resistant (RR)/multidrug-resistant (MDR)-TB cases were reported, and worldwide the treatment success rate for RR/MDR-TB was 56% in the 2016 cohort.<sup>4</sup> It is clear that to achieve the objectives of the END TB strategy, the expansion of TB control programmes, including the preventive treatment of persons at high risk, early diagnosis of TB and improvement of treatment outcomes is essential.

Because of the slow disease dynamics of TB, mathematical and computational models are useful in forecasting the long-term evolution of the TB epidemic and for planning and resource allocation in public health. Therefore, several mathematical simulation models have been combined to predict the effect of public health interventions on TB control programmes.<sup>5-7</sup> However, there are few models for the prediction of drug-resistant TB epidemiology that incorporate drug-susceptible (DS)-TB. Drug-resistant TB is a significant challenge in the Korean peninsula. North Korea is one of the 30 countries with the highest TB and RR/MDR-TB burdens and the reported and estimated number of TB has increased (345/100 000 in 2010 to 513/100 000 in 2018).<sup>4</sup> Among high-income countries, South Korea also has a considerable TB burden. The reported incidence was 96.4/100 000 in 2010 and 65.9/100 000 in 2018.<sup>8</sup> Even though South Korea has achieved considerable reduction of TB in the past, TB incidence in South Korea is seven times higher than the average incidence for member countries of the Organization for Economic Co-Operation and Development.<sup>1</sup>

Recently, molecular test for rapid diagnosis of TB and rifampin resistance are rolling out globally and several studies showed promising impact of this intervention for TB and RR/MDR-TB control.<sup>9 10</sup> Also, newly introducing new drugs for RR/MDR-TB treatment such as bedaquiline and delamanid suggest possible all oral regimens and improved outcome of RR/MDR-TB.<sup>11 12</sup>

The purpose of this study was to develop a mathematical model that accounts for recent trends in DS-TB and RR/MDR-TB incidence and to predict TB burden based on the proposed optimal TB control intervention strategy in South and North Korea.

We developed a deterministic compartmental model by incorporating the recent understanding of TB epidemiology, which aims to compare various intervention scenarios in response to TB. The model allows a systemic approach to planning control strategies considering multiple aspects of TB in South and North Korea.

## METHODS

### Study design

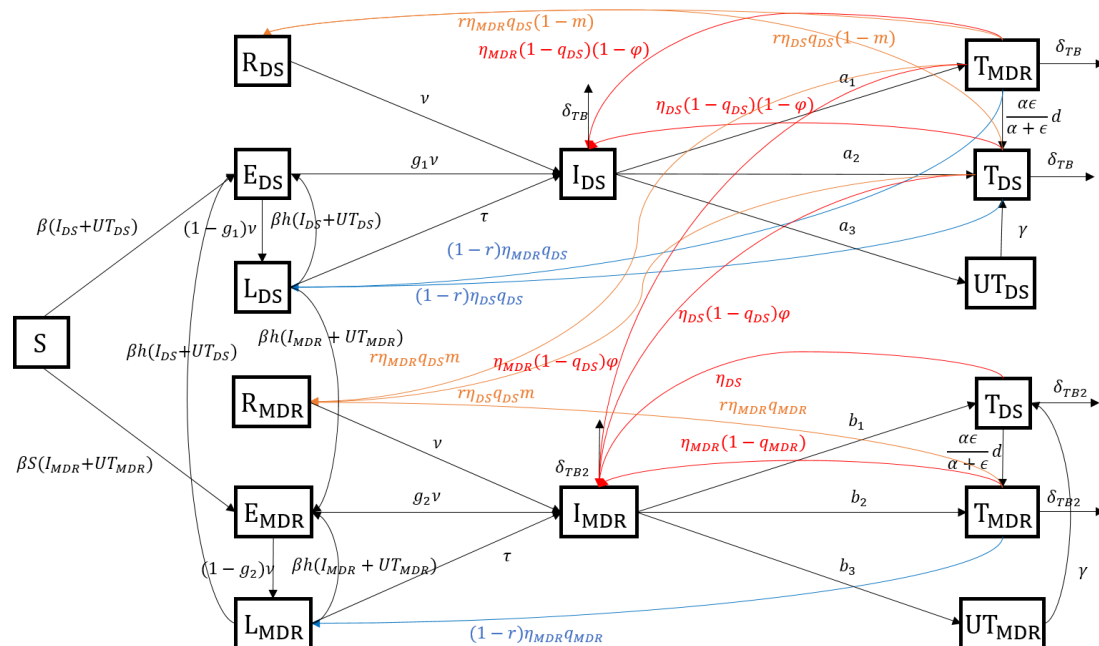
We constructed a deterministic compartmental model for TB. The basic structure of the TB model follows the Susceptible-Exposed-Infectious-Treated model but was modified by considering additional factors to reflect the characteristics of TB. We divided the latent TB infection compartment into fast progressors, E (approximately 5% of healthy adults will develop the active disease within 2 years), and slow progressors, L (individuals who do not have rapid progression). In addition, we differentiated between DS-TB and RR/MDR-TB populations to predict the long-term incidence of TB. Independent experiments were performed for South and North Korea. Our main interest is predicting the future incidence of TB and the number of TB deaths in South and North Korea by 2040. We also performed a sensitivity analysis to assess the reliability of the predictions.

### Patient and public involvement

Patients were not involved in this study.

### Mathematical model

The model population was compartmentalised and classified by the status of the disease: susceptible (S), latent infection (E and L), infectious (I), treated (T), untreated (UT) and relapsed (R). The population was also divided



**Figure 1** Diagram of TB transmission model. TB, tuberculosis.

**Table 1** Summary of parameters in South and North Korea

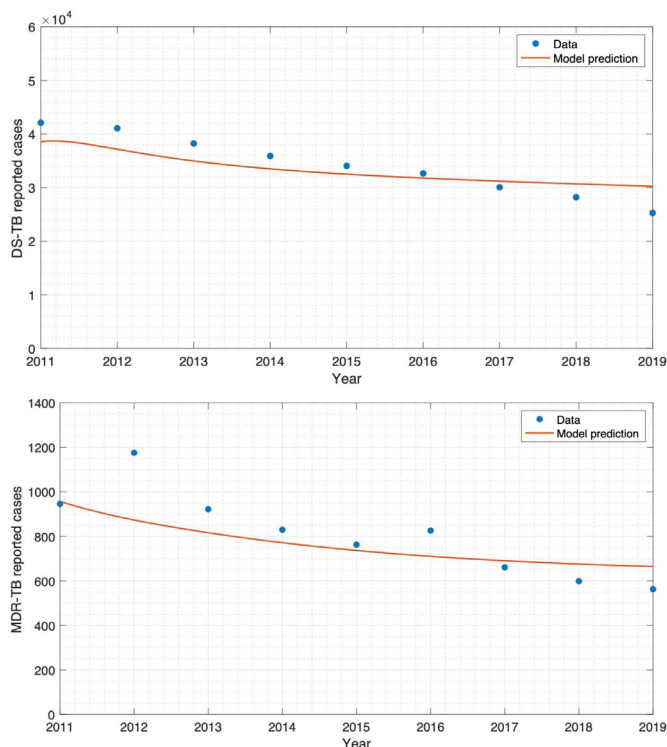
Parameters	Description	Unit	South Korea		North Korea	
			Value	Reference	Value	Reference
$\beta$	Transmission rate		5.1318e-10	Estimated	9.4297e-10	Estimated
$g_1$	Proportion of rapid progression from latent to DS-TB infectious		0.051 to 0.045	27 28	0.08	27 28
$g_2$	Proportion of rapid progression from latent to MDR-TB infectious		0.0582	27 28	0.08	27 28
$\nu$	Progression rate from the high-risk latent to the infectious state	/year	0.9	29	0.9	29
$\tau$	Progression rate from the low-risk latent to the infectious state	/year	0.00175	Estimated	0.0035	Estimated
$q_{DS}$	Proportion of DS-TB treatment success		0.925	1 30	0.85	1 30
$q_{MDR}$	Proportion of MDR-TB treatment success		0.875	1 30 31	0.8	1 30
$\eta_{DS}$	DS-TB treatment rate	/year	2	32 33	2	32 33
$\eta_{MDR}$	RR/MDR-TB treatment rate	/year	0.594	12 32	0.594	12 32
$m$	Acquired RR/MDR proportion of relapse		0.05	1 30	0.07	Assumed
$r$	Proportion of relapse after treatment success		0.05	34	0.07	Assumed
$\varphi$	Acquired RR/MDR proportion after treatment failure		0.09	1 17 30	0.12	Assumed
$\delta_1$	Death rate	/year	0.0106	35	0.0143	36
$\delta_2$	Death rate adjusted for DS-TB infected	/year	0.0163	Estimated	0.0143	Estimated
$\delta_3$	Death rate adjusted for MDR-TB infected	/year	0.0244	Estimated	0.0143	Estimated
$\delta_{TB}$	Death rate due to DS-TB infection	/year	0.1044	30 37	0.2653	Assumed
$\delta_{TB2}$	Death rate due to MDR-TB infection	/year	0.1566	30 31	0.2653	Assumed
$1/a$	Diagnostic delay	days	180	38-40	270	38-40
$a_1$	Progression rate from $I_{DS}$ to $T_{MDR}$	/year	0	13 41	0	Assumed
$a_2$	Progression rate from $I_{DS}$ to $T_{DS}$	/year	1.2167	13 41	0.6667	Assumed
$a_3$	Progression rate from $I_{DS}$ to $UT_{DS}$	/year	0.8111	13 41	0.6667	Assumed
$b_1$	Progression rate from $I_{MDR}$ to $T_{DS}$	/year	1.0342	Assumed <sup>41</sup>	0.6667	Assumed
$b_2$	Progression rate from $I_{MDR}$ to $T_{MDR}$	/year	0.1825	Assumed <sup>41</sup>	0	Assumed
$b_3$	Progression rate from $I_{MDR}$ to $UT_{MDR}$	/year	0.8111	Assumed <sup>41</sup>	0.6667	Assumed
$\gamma$	Treatment rate for untreated infectious UT	/year	12.1667	13	9.125	Assumed
$\gamma$	Drug susceptibility test rate	/year	7.3	42-44	7.3	42-44
$\alpha$	Sputum culture rate	/year	9.1250	42-44	9.1250	42-44
$d$	Proportion of drug susceptibility test implementation		0.9	Assumed	0.75	Assumed
$h$	1-partial immunity in low-risk latent state		0.35	6	0.35	6

DS, drug-susceptible ; MDR, multidrug-resistant; TB, tuberculosis.

according to susceptibility to TB drugs (DS or RR/MDR). **Figure 1** shows a flow diagram of a dynamic TB transmission model.

Briefly, the key model assumption includes all TB-infected individuals harbouring a single TB strain with a specified drug resistance pattern at any particular time. RR/MDR-TB is acquired by being infected with resistant strains, by de novo mutations during non-curative therapy, or relapse. Individuals who progress to the treatment (T) stage can be placed in three categories. The basic case of transition from the infectious state to the treated state is  $T_{DS}(a_2, b_1)$ . When patients with RR/MDR-TB are started on the DS-TB treatment ( $b_1$ ), they can move to the  $T_{MDR}$  state after drug susceptibility test results are obtained. In the second category, diagnosed patients progress to the  $T_{MDR}$  state if RR/MDR-TB is immediately diagnosed using Xpert MTB/RIF ( $b_2$ ) or if DS-TB is misdiagnosed ( $a_1$ ). Patients with misdiagnosed DS-TB can move back to the  $T_{DS}$  state with drug susceptibility test results. Progression to the untreated state (UT) occurs when the diagnosis is further delayed in the medical institutions by the AFB smear testing negative or TB-PCR ( $a_3, b_3$ ). Then, they progress to the  $T_{DS}$  state at the rate of  $\gamma$  after additional examination.

People in the slow progress latent (L) state are assumed to have partial immunity to TB, which leads to a 35% reduction in the force of infection compared with people in the susceptible (S) state.<sup>6</sup> Coinfection with HIV was not considered because such cases constitute a small proportion of all TB cases in South and North Korea.



**Figure 2** Model calibration results for South Korea. DS, drug-susceptible; MDR, multidrug-resistant; TB, tuberculosis.

### Data and parameters

The parameter values were determined using published literature reviews, estimated, derived or assumed based on the best available local epidemiological data and mathematical formulas. **Table 1** provides a summary of the descriptions and values used in the simulations.

In assessing the data of reported TB cases in South Korea, the number of reported cases is observed to have decreased rapidly since 2011. We hypothesised that this decline has been accelerated due to increased contact investigation and preventive treatment interventions compared with the previous period. Therefore, the proportion of rapid progression to active TB from the high-risk latent state has been deemed to decrease linearly between 2011 and 2019. Then, the transmission rate  $\beta$  and progression rate from slow progress latent to infectious  $\tau$  were estimated by fitting the model to the incidence data of TB in South Korea from 2011 to 2019 (**figure 2**). Maximum likelihood estimation technique was employed assuming Poisson distribution for the incidence data in model calibration.

For North Korea, the parameter values were determined similarly to those of South Korea, where global and regional WHO reports were used. The parameter values were adjusted using published literature reviews, values for South Korea and estimation based on the best available local epidemiological data.

### TB intervention strategy

#### South Korea

The proportion of high-risk, latent to active TB decreased linearly from 5.1% to 4.4% from 2011 to 2019. Reflecting this trend, an additional level of preventive therapy was imposed until the proportion reached 3.6% in 2025 for the baseline case (**table 2**).

**Scenario 1—Preventive treatment control:** Since preventive therapy affects the proportion of the high-risk latent to active TB group, we applied a gradual reduction of the flow from E to I to implement this intervention.

**Scenario 2—Diagnostic improvement:** In this scenario, the proportion of active TB would be improved with accurate diagnosis and proper treatment. This was adjusted by changing the proportion of the flow to the  $T_{MDR}$ ,  $T_{DS}$  and  $UT$  compartments. The baseline assumption was that 60% of DS-TB and 51% of MDR-TB moved to the  $T_{DS}$  state, which increased up to 80% in this scenario.

**Scenario 3—Active case-finding strategy:** The infectious period of active TB would be reduced by scaling up the discovery of active cases. Therefore, the third intervention was imposed by reducing the value of the diagnostic delay parameter for the infectious individuals to receive treatment. The baseline was assumed to be 180 days, and the intervention scenario was tested by reducing patient delay to 150 days.

**Scenario 4—Scaling up the treatment success rate for active TB:** This intervention was experimented on by changing the treatment success rate values of DS-TB and RR/MDR-TB. In the baseline case, the treatment success

**Table 2** Cumulative number of reported TB cases, annual new infection and death predictions under the baseline scenario in South Korea

	2020	2025	2030	2035	2040
Cumulative DS report	29 767	171 926	305 421	432 715	554 258
Cumulative MDR report	655	3835	6897	9885	12 810
Yearly new infection	96 825	91 372	88 220	85 548	82 925
Death by TB	4582	4248	4023	3842	3673

DS, drug-susceptible ; MDR, multidrug-resistant; TB, tuberculosis.

rates for DS-TB and RR/MDR-TB were 92.5% and 87.5%, respectively. In this scenario, the treatment success rate was increased to 97.5% for each DS-TB and RR/MDR-TB.

All interventions, except changes to the treatment success proportion, were applied simultaneously to both DS-TB and RR/MDR-TB.

### North Korea

For North Korea, all four scenarios in the South Korean intervention were similarly applied, but the model parameters for the interventions were adjusted to the North Korean situation.

### Sensitivity analysis

Sensitivity analyses were performed to examine the robustness of the model simulation results regarding the uncertainty of the parameter values. We perturbed each parameter by 5% of their values and compared the

number of DS-TB and RR/MDR-TB cases predicted in 2040.

## RESULTS

### TB cases prevented by interventions in South Korea

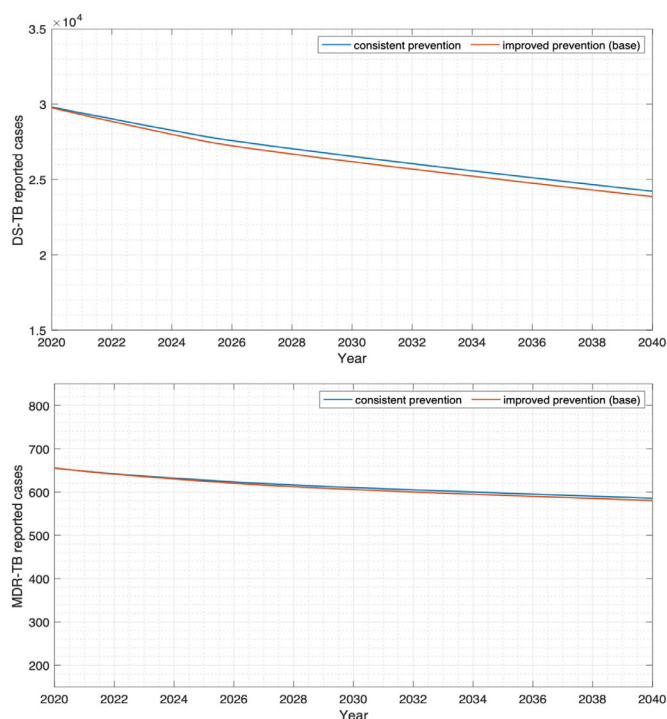
In the baseline case, the proportion of progression to active TB from the high risk latent group decreased linearly from 5.1% to 4.4% from 2011 to 2019, and an additional level of preventive therapy was imposed until the proportion reached 3.6% by 2025 (table 2). Our model projected that incident cases of DS-TB and RR/MDR-TB, respectively, would drop to 27 581 and 625 by 2025. By maintaining a consistent setting after 2025, the number of new cases of DS-TB and RR/MDR-TB decreases slightly. The impact of four different TB control strategies on the incident cases was tested based on this situation.

To investigate the effects of preventive treatment intervention, the model was simulated assuming a consistent level of preventive therapy control from 2020 for the proportion to reach 3.9% in 2025 (table 2, figure 3). Without additional preventive therapy control from 2020 to 2025, the reported TB cases increase by 356 in 2040 and 6491 cumulatively from 2020 to 2040 (table 3, figure 3).

Regarding the diagnosis improvement intervention, 60% of patients with DS-TB were treated immediately without hospital delay and, in the baseline case, the remainder had an average hospital delay of 22 days.<sup>13</sup> Only 9% of patients with RR/MDR-TB started RR/MDR-TB treatment immediately, and 51% initially received DS-TB treatment and started RR/MDR-TB treatment after the drug susceptibility test. In the diagnostic improvement control scenario, the proportion of patients without hospital delay was set at 80% for both DS-TB and RR/MDR-TB (table 4, figure 4).

As a result, it was expected to reduce, respectively, the 3287 and 2380 additional DS-TB and RR/MDR-TB cases between 2020 and 2040. The impact of diagnostic improvement was more prominent in RR/MDR-TB cases.

The effect of the active case-finding strategy was estimated by reducing the time taken until the patient is treated. The baseline value was 180 days, which was shortened to 150 days in the intervention scenario (table 5, figure 5).



**Figure 3** Number of reported TB cases with different preventive therapies implemented during 2020–2025 in South Korea. DS, drug-susceptible; MDR, multidrug-resistant; TB, tuberculosis.

**Table 3** Cumulative number of reported TB cases, annual new infection and death predictions with consistent preventive therapy from 2020 to 2025 in South Korea

	2020	2025	2030	2035	2040
Cumulative DS report	29 818	173 063	308 331	437 421	560 749
Cumulative MDR report	655	3842	6924	9937	12 888
Yearly new infection	96 986	92 391	89 400	86 735	84 112
Death by TB	4587	4290	4076	3896	3727

DS, drug-susceptible ; MDR, multidrug-resistant; TB, tuberculosis.

**Table 4** Cumulative number of reported TB cases, annual new infection and death predictions with diagnostic improvements in South Korea

	2020	2025	2030	2035	2040
Cumulative DS report	29 758	171 354	304 053	430 437	550 971
Cumulative MDR report	622	3288	5756	8131	10 430
Yearly new infection	93 907	87 752	84 616	81 962	79 355
Death by TB	4563	4161	3931	3748	3577

DS, drug-susceptible ; MDR, multidrug-resistant; TB, tuberculosis.

By reducing the delay to 150 days, the annual new infection rate significantly decreases to 64 953 in 2040, compared with 82 925 in the baseline scenario. A cumulative reduction, respectively, of 20 962 and 2584 reported DS-TB and RR/MDR-TB cases between 2020 and 2040 was expected.

Finally, the treatment success rate was improved by increasing the success rate for DS-TB from 92.5% to

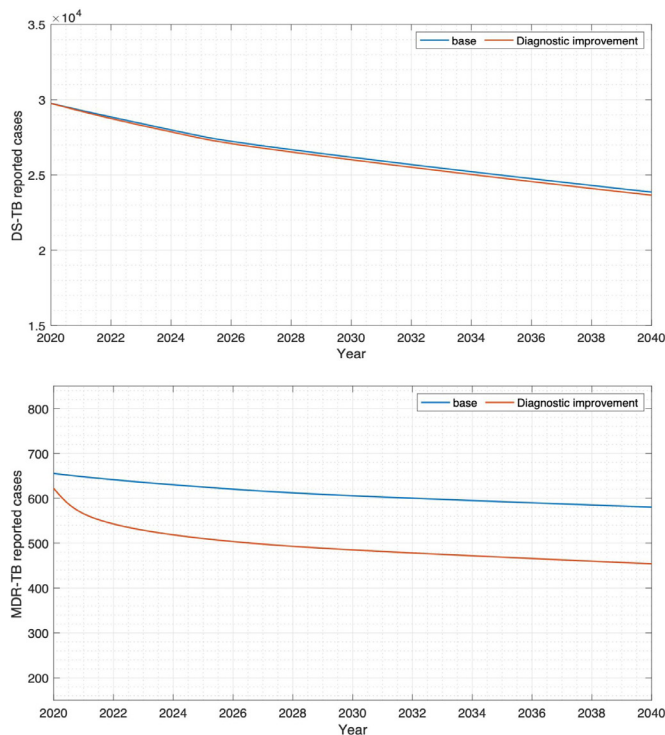
97.5% and the RR/MDR-TB success rate from 87.5% to 97.5% in a separate simulation (tables 6 and 7, figures 6 and 7). The improvement in the DS-TB treatment success rate, respectively, reduced the 25 045 and 3876 cumulative reported cases of DS-TB and RR/MDR-TB between 2020 and 2040. Conversely, the control of RR/MDR-TB only decreased DS-TB cases by 4 and RR/MDR-TB cases by 1118 cumulatively during 2020 and 2040. It was observed that amelioration of the DS-TB treatment success rate had a greater impact on both the DS-TB and RR/MDR-TB cases.

**Sensitivity analysis in South Korea**

We measured the sensitivity of the TB burden in 2040 regarding the model parameters by perturbing 5% of the value of each parameter (figure 8). While the reported cases of DS-TB were most sensitive to the progression rate from the low-risk latent to infectious, MDR-TB was most sensitive to the proportion of DS treatment success. Diagnostic delay and transmission rate played key roles in both DS and MDR infection dynamics. The proportion of successful DS treatments, death rate adjusted for DS infection and the proportion of rapid progression from latent to DS-infectious were also significant in the results of the DS-TB cases. The MDR-TB cases were highly sensitive to the progression rate from the low-risk latent to infectious and the proportion of successful MDR treatments.

**Prevented TB cases by interventions and sensitivity analysis in North Korea**

The number of reported incident cases for DS-TB and estimated incident cases for RR/MDR-TB slightly increased from 2012 to 2015 and decreased from 2015 to 2019 in North Korea. All parameters were assumed to



**Figure 4** Number of reported TB cases with diagnostic improvement in South Korea. DS, drug-susceptible; MDR, multidrug-resistant; TB, tuberculosis.

**Table 5** Cumulative number of reported TB cases, annual new infection and death predictions with active case-finding in South Korea

	2020	2025	2030	2035	2040
Cumulative DS report	31 909	170 422	298 130	418 910	533 296
Cumulative MDR report	696	3430	5810	8066	10 226
Yearly new infection	86 530	73 117	70 073	67 486	64 953
Death by TB	4308	3395	3174	3005	2847

DS, drug-susceptible ; MDR, multidrug-resistant; TB, tuberculosis.

**Table 6** Cumulative number of reported TB cases, annual new infection and death predictions with improvement of treatment success rate for DS-TB in South Korea

	2020	2025	2030	2035	2040
Cumulative DS report	29 059	165 060	292 373	413 612	529 213
Cumulative MDR report	582	2925	5014	7008	8934
Yearly new infection	94 356	86 737	83 625	80 986	78 394
Death by TB	4514	4015	3790	3612	3446

DS, drug-susceptible ; MDR, multidrug-resistant; TB, tuberculosis.

**Table 7** Cumulative number of reported TB cases, yearly new infection and death predictions with improvement of treatment success rate for MDR-TB in South Korea

	2020	2025	2030	2035	2040
Cumulative DS report	29 762	171 915	305 410	432 707	554 254
Cumulative MDR report	632	3563	6349	9054	11 692
Yearly new infection	96 735	91 194	88 040	85 365	82 737
Death by TB	4579	4233	4008	3827	3658

DS, drug-susceptible ; MDR, multidrug-resistant; TB, tuberculosis.

be constant from 2012 to 2019. Assuming all parameters remain constant, new cases of DS-TB decreased slightly, but cases of RR/MDR-TB were expected to increase gradually (online supplemental table S1).

The impact was assessed of four different TB control strategies on the incident cases, taking this situation as a baseline. The qualitative results are similar to South Korea in general. Please refer to online supplemental tables S1-1–S1-5 and figures S3–S6 for details.

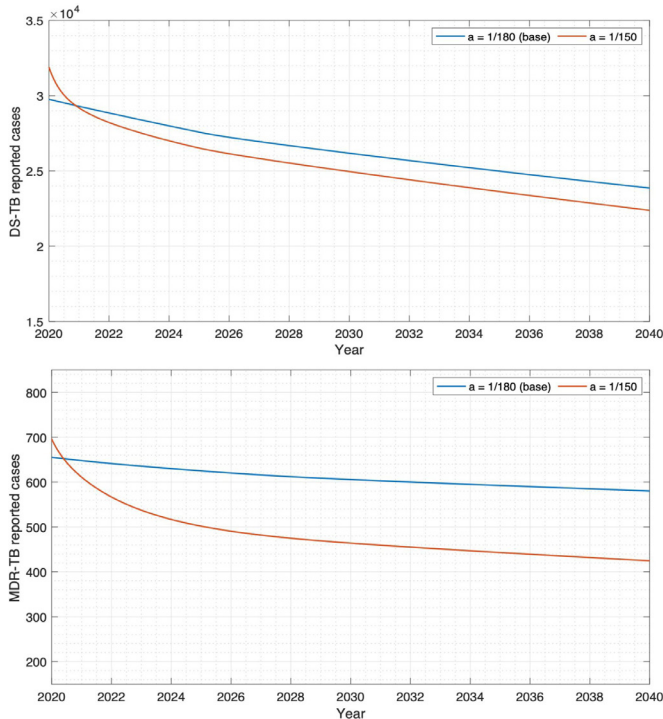
We performed a sensitivity analysis of the TB burden in 2040 regarding model parameters in the same way as in South Korea (online supplemental figure S7). The results are almost identical in that the progression rate from the low-risk latent to infectious, the proportion of DS treatment success, diagnostic delay and transmission rate played significant roles in the DS-TB and MDR-TB infection dynamics.

## DISCUSSION

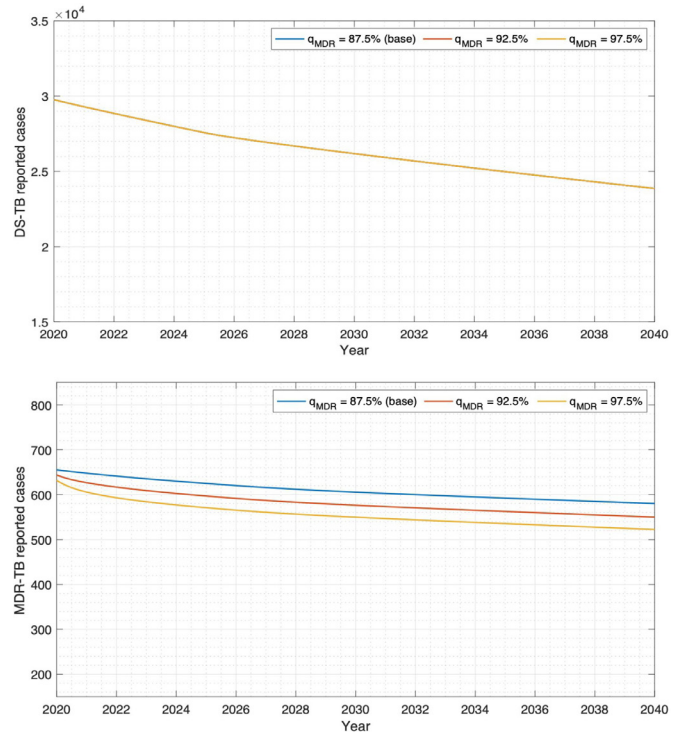
New DS-TB and MDR-TB cases in Korea have steadily declined from 2011 to the present. According to the 2018 Tuberculosis Annual Report,<sup>8</sup> the number of new patients with pulmonary TB decreased from 30 100 new

cases in 2011 to 20 883 new cases in 2018. While the steady TB control strategy has reduced the TB incidence, based on the results of the simulation using a mathematical model, in the long term, the current decline is not expected to continue. By maintaining the current level of preventive control strategy until 2025, new TB cases are expected to decrease by only 14.5% from 2019 to 2040, contrasted with the 19.9% reduction between 2011 and 2019. The long-term incubation period of TB is believed to be responsible for this mitigation. The latent TB infection rate among Koreans is 33.2%, which is approximately 17 million people as of 2016.<sup>14</sup> Our model simulations predicted that the number of people in the low-risk latent compartment would decrease very slowly. This is because none of the major TB control strategies directly target low-risk latent groups.

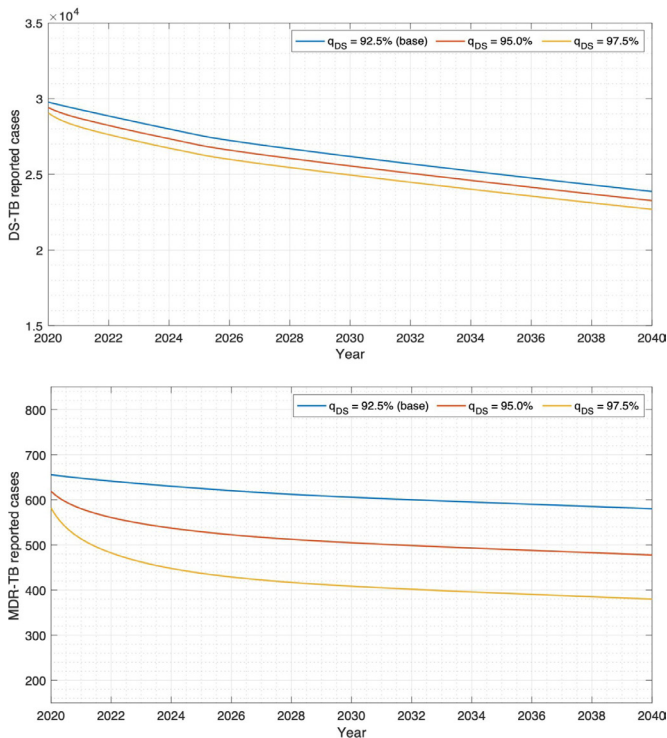
Contact investigation and preventive therapy for the close contact group had a significant impact on the reduction of new TB cases from 2011 to 2019. However, the long-term impact of preventive therapy for close contacts is not expected to be as effective as currently, due to TB having a long incubation period and a considerable population being latently infected in South Korea.



**Figure 5** Number of reported TB cases with active case-finding in South Korea. DS, drug-susceptible; MDR, multidrug-resistant; TB, tuberculosis.



**Figure 7** Number of reported TB cases with improvement of treatment success rate for RR/MDR-TB in South Korea. DS, drug-susceptible; MDR, multidrug-resistant; RR, rifampin-resistant; TB, tuberculosis.

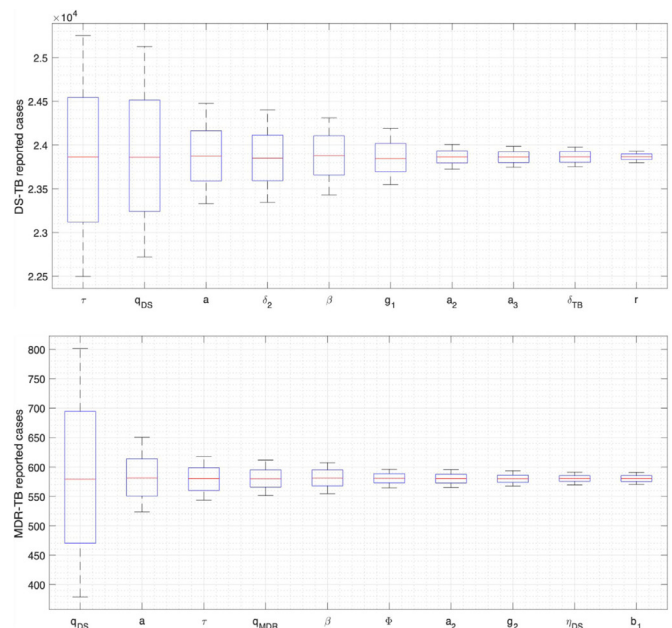


**Figure 6** Number of reported TB cases with improvement of treatment success rate for DS-TB in South Korea. DS, drug-susceptible; MDR, multidrug-resistant; TB, tuberculosis.

2011 to 2019 was 19.9%. Thus, a comprehensive TB control strategy is required to achieve the TB elimination goal in South Korea.

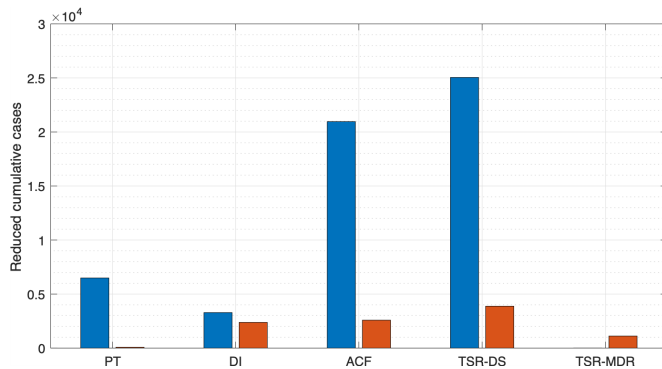
The quick and accurate diagnosis of TB and drug resistance was found to be more effective for RR/MDR-TB than for DS-TB. This is because, at the baseline, only

Implementing the preventive therapy control from 2020 to 2025, 1.5 times the level of control during the period from 2011 to 2019, the decrease in new TB cases from 2019 to 2025 was only 8.5%, while the reduction from



**Figure 8** Sensitivity analysis of TB burden in 2040 regarding model parameters in South Korea. DS, drug-susceptible; MDR, multidrug-resistant; TB, tuberculosis.





**Figure 9** Reduction of cumulative TB cases from 2020–2040 under different intervention scenarios compared to the baseline in South Korea. Blue and red represent reductions in DS-TB and RR/MDR-TB cases, respectively. ACF, Active case-finding; DI, Diagnostic improvement; PT, Preventive treatment; TSR-DS, Treatment success rate for DS-TB; TSR-MDR, Treatment success rate for RR/MDR-TB.

9% of RR/MDR-TB cases are treated immediately without hospital delay; diagnosis of RR/MDR-TB can be improved more than for than DS-TB. This implies that the scale-up of rapid RR/MDR-TB diagnostic capacities such as rolling out of the Xpert MTB/RIF assay can help to reduce the number of cases of RR/MDR-TB in South Korea.

Worldwide, early case-finding and effective treatment are the principal strategies for controlling TB transmission and reduce incidence.<sup>15 16</sup> The improvement in the treatment success rate and the active case-finding strategy were found to have the most immediate effect among the interventions in our study (figure 9). The higher treatment success rate was substantially effective and meaningful in terms of RR/MDR-TB control in particular. The estimated proportion of TB cases with RR/MDR was 9.2% among previously treated cases in South Korea, which increased to 25% among re-treatment cases after treatment failure.<sup>4 17</sup> If the treatment success rate for DS-TB increases, then the number of re-treatment patients decreases, which reduces the number of patients with RR/MDR-TB. The other policy is expected to decrease the number of low-risk latent groups in the long term by reducing the infectious period of TB, which significantly curbs new infections.

Estimated data on reported TB cases in North Korea show that incidence rates remained constant between 2012 and 2019<sup>4 18</sup> and preventive treatment strategy may be implemented in children under 5 years in familial contact based on WHO recommendation<sup>19</sup> in North Korea. It might take time to implement active contact investigation and preventive treatment for all age in North Korea. Therefore, in the North Korean baseline scenario, preventive therapy control was assumed to remain constant from 2012 to 2040. Some parameters used in the North Korean model were determined in consideration of the resource limited situation in health system, malnutrition and high smoking rate compared with South Korea. Under these assumptions,

it is predicted that the number of new TB cases will not decrease significantly.

In North Korea, the active case-finding was found to be most effective followed by preventive treatment. In our predicted model, RR/MDR-TB cases consistently would be a huge burden in North Korea. In fact, the diagnostic and treatment capacities for RR/MDR-TB in North Korea are scarce. The Ministry of Public Health of North Korea first began diagnosing and treating MDR-TB in 2008 with support from the Eugene Bell Foundation (EBF), a non-governmental organisation.<sup>20</sup> However, the EBF programme did not cover all of North Korea. In 2010, the Global Fund to Fight AIDS, TB, and Malaria (GFATM) began a major project to strengthen TB control in North Korea,<sup>21</sup> but a small portion of this international aid was allocated for the treatment of drug-resistant TB.<sup>22</sup> In addition, the tight UN sanctions due to the nuclear programme of North Korea have made it difficult to maintain the humanitarian assistance operations for the management of TB and MDR-TB in North Korea.<sup>23</sup> In fact, GFATM closed its grant for North Korea in June 2018 and reached new agreement in 2020.<sup>24</sup> North Korea is one of the high burden country of both TB and RR/MDR-TB.<sup>4</sup> Unstable drug supply and delayed diagnosis of TB and drug resistance would further increase the development of drug resistance in North Korea. Even in our model, which assumed the stable supply of TB drugs and diagnostics, RR/MDR-TB in North Korea increased in 2040. Thus, to overcome the burden of RR/MDR-TB in North Korea, a sustainable and comprehensive TB control strategy that focuses on both DS-TB and RR/MDR-TB is necessary.

### Limitations

Despite the strengths, this study has several limitations. First, age was not considered in the model to describe TB infection dynamics. Progression rate from latent state to active infectious state in TB and death rate may differ according to age.<sup>25</sup> Second, it is assumed that infectivity remains constant during patient delay. However, the infectivity of TB can vary depending on the degree of disease progression and coughing and may not be constant during the patient delay period. Third, we hypothesised that decline of TB cases has been accelerated due to increased contact investigation and preventive treatment interventions to calibrate the model. However, the source actions of the current trend of decreasing number of new TB cases are unclear, since South Korea has carried out several interventions simultaneously to reduce the incidence of TB. Some other factors, including patient delay, hospital delay and low-risk latent to infectious, may have contributed to the reduction in TB cases during this period. In addition, there was an expansion of universal health coverage for TB treatment as social protection and strengthening the occupational health programme for TB. However, due to the lack of evidence for the impact of these factors on TB incidence, they were considered constant. Fourth, external aspects of the disease, such as changes in disease-related perceptions,

were not considered. Research on TB awareness showed that the rate of willingness to screen for TB improved from 53.2% in 2013 to 62.7% in 2015.<sup>26</sup> This suggests that apart from direct interventions, improved awareness can also decrease patient delay. Finally, the values of many parameters were assumed because of the lack of available information in North Korea.

## CONCLUSION

The results show that intervention strategies in the order of improvement of treatment success rate for DS-TB, active case-finding, preventive therapy, reduced hospital delay and improvement of treatment success rate for RR/MDR-TB in South Korea are effective (figure 9). In particular, the treatment success rate increment for DS-TB has the most effect in reducing RR/MDR-TB. In North Korea, active case finding has the greatest impact on new TB incidence followed by the preventive therapy and treatment success rate for DS-TB (figure 8).

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